Altered dietary salt intake for chronic kidney disease (Protocol)

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[Intervention Protocol]

Altered dietary salt intake for chronic kidney disease

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

This review will aim to evaluate the benefits and harms of altering dietary salt intake for people with CKD.

BACKGROUND

Description of the condition

Chronic kidney disease (CKD) is a major public health problem worldwide; data from Australia, the United States, Japan, and Europe indicate that CKD occurs in 6% to 13% of people in these populations (Chadban 2003; Coresh 2007; El Nahas 2005; Hamer 2006). Evidence indicates that the prevalence of CKD is rapidly increasing, which is at least partially explained by dramatic increases in rates of diabetes and hypertension, two of the most common causes of CKD (Coresh 2007). CKD is a progressive condition. Once patients reach end-stage kidney disease (ESKD), dialysis or transplantation is required to survive. In people with ESKD, risk of mortality is 40 times that of the general population (Collins 2003), and the annual cost of care is increased approximately 10-fold compared with CKD management (Hunsicker 2004).
CKD is also an independent risk factor for cardiovascular disease; people with CKD are 5 to 10 times more likely to die of cardiovascular disease than progress to ESKD (Go 2004). Because both cardiovascular disease and progression to ESKD may be delayed, or possibly prevented, effective strategies to reduce these outcomes are needed to improve patient prognosis and reduce healthcare costs attributable to this population.

Description of the intervention

Excessive salt (sodium) intake is related to many risk factors for cardiovascular disease and CKD progression including increased blood pressure, fluid retention, proteinuria, inflammation, oxidative stress and endothelial dysfunction (Al-Solaiman 2009; Ritz 2009). Salt restriction has been shown to have a beneficial effect against risk factors such as hypertension and proteinuria, over and above that provided by antihypertensive medications (Vogt 2008). Despite this, evidence suggests salt restriction is not adequately emphasised for people with CKD (Thijssen 2008). One of the reasons for this may be that there is no clear consensus on the benefits of reducing salt intake in people with CKD. Evidence-based practice guidelines show inconsistencies in the ideal target for salt intake in people with CKD, with salt targets ranging from less than 3.8 g of salt (65 mmol sodium) per day to 6.5 g (110 mmol sodium) per day (Ash 2006; USDA 2010).

How the intervention might work

Studies in the general population have consistently demonstrated the link between dietary salt and blood pressure, particularly in those who are 'salt sensitive' (He 2004; Svetkey 1999). A recent meta-analysis on reducing salt intake in people with diabetic kidney disease also showed considerable blood pressure reductions; systolic/diastolic blood pressure was lowered by 7/3 mm Hg (Suckling 2010).

New evidence suggests salt has adverse effects independent of blood pressure. Todd 2010 found arterial stiffness measured by pulse wave velocity was significantly decreased independently of blood pressure changes in hypertensive patients on a low salt diet. Increased pulse wave velocity is a predictor of all-cause and cardiovascular mortality (Guerin 2001). Proteinuria, a risk factor for both CKD progression and cardiovascular disease in people with CKD, has also shown to be reduced by salt restriction independent of blood pressure (Verhave 2004).

Why it is important to do this review

Salt intake shows great promise as a modifiable risk factor for the reduction in cardiovascular risk and CKD progression even in very early stages of the disease. However, clear consensus of the benefits of reducing salt in people with CKD, and the optimal target salt intake for this population, has yet to be established. This review will evaluate the benefits and harms of altering dietary salt intake in people with CKD, to reduce uncertainty and facilitate best practice for managing salt intake for people with CKD.

OBJECTIVES

This review will aim to evaluate the benefits and harms of altering dietary salt intake for people with CKD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) measuring the effect of a low versus high salt intake in people with CKD will be included.

Types of participants

Inclusion criteria

- Participants with CKD (as defined by Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines) at all stages (NKF 2002)
- Aged 18 years or over.

Exclusion criteria

- Pregnant women
- Children (aged up to 18 years).

Types of interventions

- Studies that compare two or more differing sodium intakes.
- Study period of at least one week.
- Sodium intake estimated by 24 hour urinary sodium excretion (24 h UNa) with a minimum difference in 24 h UNa of 34 mmol (2 g salt/d) achieved between allocated interventions. Reduction in 24 h UNa will be calculated as the difference between the UNa at the end of each intervention for cross-over studies, and the difference in change between groups from baseline to the end of intervention for parallel studies.
- We will included studies where concomitant interventions such as antihypertensive medication or other dietary modifications were used during the study period, providing that these interventions were constant throughout the low and high salt interventions.

Types of outcome measures

Primary outcomes

1. Cardiovascular mortality
2. All-cause mortality.

Secondary outcomes

1. Cardiovascular disease (coronary artery disease, heart failure, cerebrovascular disease and peripheral vascular disease)
2. Progression to ESKD requiring dialysis or transplantation
3. Change in blood pressure (clinic and ambulatory)
4. Change in arterial stiffness (pulse wave velocity and augmentation index)
5. Change in renal function measures (creatinine clearance, serum creatinine, proteinuria, glomerular filtration rate)
6. Change in markers of fluid overload (brain natriuretic peptide, weight, bio-impedance analysis)
7. Change in markers of oxidative stress or inflammation (C-reactive protein, adipokines)

8. Adverse events: Hypotensive episodes, undesirable change in blood lipids (low density lipoprotein, high-density lipoprotein).

Search methods for identification of studies

Electronic searches

We will search the Cochrane Renal Group's Specialised Register through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from sources.

- Quarterly searches of the Cochrane Central Register of Controlled Trials CENTRAL
- Weekly searches of MEDLINE OVID SP
- Handsearching of renal-related journals and the proceedings of major renal conferences
- Searching of the current year of EMBASE OVID SP
- Weekly current awareness alerts for selected renal journals
- Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies as well as a list of handsearched journals, conference proceedings and current awareness alerts are available in the Specialised Register section of information about the Cochrane Renal Group. See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of nephrology textbooks, review articles and relevant studies.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by two authors, who will discard studies that are not applicable; however, studies and reviews that might include relevant data or information on studies will be retained initially. Two authors will independently assess retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria.

Data extraction and management

Data extraction will be carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one study exists, reports will be grouped together and the publication with the most complete data will be used in the analyses. Where relevant outcomes are only published in earlier versions these data will be used. Any discrepancy between published versions will be highlighted.

Assessment of risk of bias in included studies

The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (*see* Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
    - Participants and personnel
    - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (cardiovascular mortality, all-cause mortality, progression to ESKD, cardiovascular disease) results will be expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (blood pressure, pulse wave velocity, augmentation index, creatinine clearance, serum creatinine, proteinuria, glomerular filtration rate, brain natriuretic peptide, weight, bio-impedance analysis, C-reactive protein, adipokines) the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used. Studies analysing change scores will be included in meta-analysis along with studies including the endpoint data only.

Where change from baseline values are absent, these will be calculated by subtracting mean value at the end of the intervention to baseline values (parallel studies) or subtracting the value from the end of the higher sodium phase from the lower sodium phase (cross-over studies). Standard deviations for change may be imputed where appropriate using the methods outlined in the Cochrane Handbook (Higgins 2011).

When investigating time-to-event data (i.e. survival), a summary of the outcomes will be made using Kaplan-Meier analysis with the intervention effect expressed as a hazard ratio (Higgins 2011)

Unit of analysis issues

In cross-over studies, we will determine the MD in outcomes as the difference between the end of the low salt period and the end of the high salt period. For parallel studies we will calculate the treatment effect as the difference between the two treatment groups in the change in outcomes from baseline.

Dealing with missing data

Any further information required from the original author will be requested by written correspondence (e.g. emailing and/or writing to corresponding author/s) and any relevant information obtained in this manner will be included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population will be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals will be investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) will be critically appraised (Higgins 2011).

Assessment of heterogeneity

Heterogeneity will be analysed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test (Higgins 2003). I² values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Data will be pooled using the random-effects model but the fixed-effect model will also be used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore possible sources of heterogeneity (e.g. intervention duration, levels of sodium intake). Heterogeneity among participants could be related to age, stage of CKD, presence of comorbidities (e.g. hypertension and diabetes) and renal pathology (e.g. dialysed versus non-dialysed patients with CKD).

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of the following factors on effect size:

- repeating the analysis excluding unpublished studies
- repeating the analysis taking account of risk of bias, as specified
- repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

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REFERENCES

Additional references

Al-Solaiman 2009
Al-Solaiman Y, Jesri A, Zhao Y, Morrow JD, Egan BM. Low-Sodium DASH reduces oxidative stress and improves vascular function in salt-sensitive humans. *Journal of Human Hypertension* 2009;**23**(12):826–35. [MEDLINE: 19404315]

Ash 2006
Ash S, Campbell K, MacLaughlin H, McCoy E, Chan M, Anderson K, et al.Evidence based practice guidelines for the nutritional management of chronic kidney disease. *Nutrition & Dietetics* 2006;**63**(Suppl s2):S33–S45. [DOI: 10.1111/j.1747-0080.2006.00100.x]

Chadban 2003
Chadban SJ, Briganti EM, Kerr PG, Dunstan DW, Welborn TA, Zimmet PZ, et al.Prevalence of kidney damage in Australian adults: The AusDiab kidney study. *Journal of the American Society of Nephrology* 2003;**14**(7 Suppl 2):S131–8. [MEDLINE: 12819318]

Collins 2003
Collins AJ, Li S, Gilbertson DT, Liu J, Chen SC, Herzog CA. Chronic kidney disease and cardiovascular disease in

the Medicare population. *Kidney International - Supplement* 2003, (87):S24–31. [MEDLINE: 14531770]

Coresh 2007
Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al.Prevalence of chronic kidney disease in the United States. *JAMA* 2007;**298**(17):2038–47. [MEDLINE: 17986697]

El Nahas 2005
El Nahas AM, Bello AK. Chronic kidney disease: the global challenge. *Lancet* 2005;**365**(9456):331–40. [MEDLINE: 15664230]

Go 2004
Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *New England Journal of Medicine* 2004;**351**(13):1296–305. [MEDLINE: 15385656]

Guerin 2001
Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001;**103**(7):987–92. [MEDLINE: 11181474]

Hamer 2006
Hamer RA, El Nahas AM. The burden of chronic kidney disease. *BMJ* 2006;**332**(7541):563–4. [MEDLINE: 16528062]

He 2004
He FJ, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database of Systematic Reviews* 2004, Issue 1. [DOI: 10.1002/14651858.CD004937]

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557–60. [MEDLINE: 12958120]

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hunsicker 2004
Hunsicker LG. The consequences and costs of chronic kidney disease before ESRD. *Journal of the American Society of Nephrology* 2004;**15**(5):1363–4. [MEDLINE: 15100382]

NKF 2002
National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *American Journal of Kidney Diseases* 2002;**39**(2 Suppl 1):S1–266. [MEDLINE: 11904577]

Ritz 2009
Ritz E, Koleganova N, Piecha G. Role of sodium intake in the progression of chronic kidney disease. *Journal of Renal Nutrition* 2009;**19**(1):61–2. [MEDLINE: 19121773]

Suckling 2010
Suckling RJ, He FJ, Macgregor GA. Altered dietary salt intake for preventing and treating diabetic kidney disease. *Cochrane Database of Systematic Reviews* 2010, Issue 12. [DOI: 10.1002/14651858.CD006763.pub2]

Svetkey 1999
Svetkey LP, Simons-Morton D, Vollmer WM, Appel LJ, Conlin PR, Ryan DH, et al.Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. *Archives of Internal Medicine* 1999;**159**(3):285–93. [MEDLINE: 9989541]

Thijssen 2008
Thijssen S, Kitzler TM, Levin NW. Salt: its role in chronic kidney disease. *Journal of Renal Nutrition* 2008;**18**(1):18–26. [MEDLINE: 18089439]

Todd 2010
Todd AS, Macginley RJ, Schollum JB, Johnson RJ, Williams SM, Sutherland WH, et al.Dietary salt loading impairs arterial vascular reactivity. *American Journal of Clinical Nutrition* 2010;**91**(3):557–64. [MEDLINE: 20107199]

USDA 2010
US Department of Agriculture and US Department of Health and Human Services Services. Dietary Guidelines for Americans, 2010. 7th edition. http://www.cnpp.usda.gov/DGAs2010-PolicyDocument.htm (accessed 9 July 2012).

Verhave 2004
Verhave JC, Hillege HL, Burgerhof JG, Janssen WM, Gansevoort RT, Navis GJ, et al.Sodium intake affects urinary albumin excretion especially in overweight subjects. *Journal of Internal Medicine* 2004;**256**(4):324–30. [MEDLINE: 15367175]

Vogt 2008
Vogt L, Waanders F, Boomsma F, de Zeeuw D, Navis G. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. *Journal of the American Society of Nephrology* 2008;**19**(5):999–1007. [MEDLINE: 18272844]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. sodium chloride:kw 2. ((sodium or salt) near/5 (low or high or alter* or reduce* or reducing or reduction or restrict* or intake* or diet* or increas* or decreas* or change* or changing)):ti,ab,kw 3. (#1 OR #2) 4. "renal replacement therapy":ti,ab,kw 5. (h*emodialysis or h*emofiltration or h*emodiafiltration):ti,ab,kw 6. dialysis:ti,ab,kw 7. (CAPD or CCPD or APD):ti,ab,kw 8. ("kidney disease" or "kidney diseases" or "renal disease" or "renal diseases"):ti,ab,kw 9. (chronic next kidney or chronic next renal):ti,ab,kw 10. ((kidney next failure) or (renal next failure)):ti,ab,kw 11. ("end-stage kidney" or "end-stage renal" or "endstage kidney" or "endstage renal"):ti,ab,kw 12. (ESRF or ESKF or ESRD or ESKD):ti,ab,kw 13. (CKF or CKD or CRF or CRD):ti,ab,kw 14. (predialysis or "pre-dialysis"):ti,ab,kw 15. (nephropath* or nephrit* or glomerulo*):ti,ab,kw 16. (glomerular next disease*):ti,ab,kw 17. (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16) 18. (#3 AND #17)
MEDLINE	1. exp Sodium Chloride/ 2. Diet, Sodium Restricted/ 3. ((sodium or salt) adj5 (low or high or alter* or reduce* or reduction or restrict* or intake* or diet* or increas* or decreas* or change* or changing)).tw. 4. or/1-3 5. Renal Replacement Therapy/ 6. exp Renal Dialysis/ 7. (hemodialysis or haemodialysis).tw. 8. (hemofiltration or haemofiltration).tw. 9. (hemodiafiltration or haemodiafiltration).tw. 10. dialysis.tw. 11. (CAPD or CCPD or APD).tw. 12. exp Kidney Diseases/ 13. (kidney disease* or renal disease*).tw. 14. (nephropath* or nephrit* or glomerulo* or glomerular disease*).tw. 15. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 16. (ESRF or ESKF or ESRD or ESKD).tw. 17. (chronic kidney or chronic renal).tw. 18. (CKF or CKD or CRF or CRD).tw. 19. (predialysis or pre-dialysis).tw. 20. or/5-19 21. and/4,20

(*Continued*)

EMBASE	1. Sodium Chloride/ 2. Salt Intake/ 3. Sodium Restriction/ 4. Sodium Intake/ 5. ((sodium or salt) adj5 (low or high or alter* or reduce* or reduction or restrict* or intake* or diet* or increas* or decreas* or change* or changing)).tw. 6. or/1-5 7. exp Renal Replacement Therapy/ 8. (hemodialysis or haemodialysis).tw. 9. (hemofiltration or haemofiltration).tw. 10. (hemodiafiltration or haemodiafiltration).tw. 11. dialysis.tw. 12. (CAPD or CCPD or APD).tw. 13. exp Kidney Disease/ 14. (kidney disease* or renal disease*).tw. 15. (nephrop* or nephrit* or glomerulo* or glomerular disease*).tw. 16. (chronic kidney or chronic renal).tw. 17. (CKF or CKD or CRF or CRD).tw. 18. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 19. (ESRF or ESKF or ESRD or ESKD).tw. 20. (predialysis or pre-dialysis).tw. 21. or/7-20 22. and/6,21

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inade-	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention

(*Continued*)

quate concealment of allocations prior to assignment	group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome

(*Continued*)

	data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.

(*Continued*)

	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

HISTORY

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CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: EMc, KC, JB, DM
2. Study selection: EMc, KC, JB
3. Extract data from studies: EMc, KC
4. Enter data into RevMan: EMc, KC
5. Carry out the analysis: EMc, KC
6. Interpret the analysis: EMc, KC, JB, DM
7. Draft the final review: EMc, KC, JB, DM
8. Disagreement resolution: DM
9. Update the review: EMc, KC

DECLARATIONS OF INTEREST

- Emma J McMahon: none known
- Katrina L Campbell: none known
- Judith D Bauer: none known
- David W Mudge: none known

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Internal sources

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- University of Queensland, Australia.

Salary (JB, EH)

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